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Traumatic Stress Interacts With Bipolar Disorder Genetic Risk to Increase Risk for Suicide Attempts

RH = Trauma, Genetic Risk and Suicide Attempts

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ABSTRACT

Objective: Bipolar disorder (BD) is one of the most heritable psychiatric conditions and is associated with high suicide risks. To explore the reasons for this link, we examine the interaction between traumatic stress and BD polygenic risk score in relation to suicidal ideation, suicide attempt and non-suicidal self-injury (NSSI) among adolescent/young adult offspring and relatives of persons with BD ("BD-relatives") and adolescent/young adult offspring of individuals without psychiatric disorders ("controls").

Method: Data were collected from four sites in the US and one in Australia during 2006-2012. Generalized estimating equation models were used to compare rates of ideation, attempts, and NSSI between BD-relatives (n=307) and controls (n=166), while also studying the contribution of demographic factors, traumatic stress exposure, lifetime mood or substance (alcohol/drug) use disorders, and BD polygenic risk score.

Results: After adjusting for demographic characteristics and mood and substance use disorders, BD-relatives were at increased risk for ideation and attempts, but not NSSI. Independent of BD-relative/control status, demographic factors, mood and substance use disorders, exposure to trauma within the past year (including bullying, sexual abuse, and domestic violence) was associated with suicide attempt (p=.014), and BD polygenic risk score was also marginally associated with attempts (.061). Importantly, the interaction between BD polygenic risk score and traumatic event exposures was significantly associated with attempts, independent of demographics, relative/control status, and mood and substance use disorders (p=.037).

Conclusion: BD-relatives are at increased risk for suicide attempts and ideation, especially if they are exposed to trauma and have evidence of increased genetic vulnerability.

Key words: bipolar disorder; suicide, attempted; populations at risk; polygenic risk; traumatic

stress

INTRODUCTION

Individuals with bipolar disorder (BD) are at high risk for suicide attempts and suicide death.[1] As many as 20-25% of individuals with a clinical diagnosis of BD die by suicide.[2,3] A systematic review by Tondo[4] reported that in 101 published studies from 22 countries (N=80,000), 31% of those with BD made at least one lifetime suicide attempt, versus 4% of community-residing adults. Simon et al.[5] noted the relatively low suicide attempt to suicide death ratio within persons with BD as compared to the general population, which suggests stronger suicide intent and higher lethality of methods.

Although an earlier onset of BD is associated with increased risk of suicidal behaviors,[6] ideation and attempts remain significantly under-researched in adolescents and young adults at high familial risk for BD, particularly in genetically informative samples with prospective longitudinal designs. Two studies of youth at risk for BD have reported elevated rates of ideation and attempts. Klimes-Dougan[7] found that BD offspring at the average age of 22 years were at higher risk for suicide plans and attempts than offspring of parents with major depressive disorder (MDD) and offspring of well parents; however, that study had a small sample size of 37 BD offspring. Goldstein,[8] using data from the Pittsburgh Bipolar Offspring Study (BIOS)[9] of 388 offspring (ages 6-18 years) of 233 parents with bipolar I (BP-I) or bipolar II (BP-II) as well as 250 offspring of matched control parents, found that BD offspring had significantly elevated rates of ideation (33% vs. 20%; OR=2.1).

Studies have found that as many as 50% of adults with BD report a history of childhood abuse,[10-14] and many studies report that adults with BD who experienced child physical or sexual abuse were younger at BD symptom onset and experienced a worse clinical course compared to

those without abuse.[10-12, 15] In a systematic review of childhood maltreatment in BD, Agnew-Blais and Danese[16] found that maltreatment was associated with several negative clinical outcomes, including suicide attempts, and might be an early indicator of a particularly unfavorable clinical course.

The stress–diathesis model of suicidal behavior[17] describes suicidal behaviors to be the result of an interaction between state-dependent stressors and a trait-like susceptibility to suicidal behavior that includes both familial and genetic factors. Indeed, offspring of parents with BD may have biological vulnerabilities that increase their risk for depression and suicide,[18] but may also experience disruptive home environments including exposure to parental suicidal behaviors.[19,20]

A number of studies have attempted to map specific genetic variants underlying suicidal behaviors, using approaches both within and across psychiatric diagnoses, so far with limited success (reviewed in Sokolowski[21]). This is largely due to the relatively small sample sizes hitherto examined (typically <5,000 individuals with suicide attempt data). However, as with the genetic architecture of psychiatric diagnoses,[22,23] susceptibility to ideation and attempt appears to be highly polygenic.[24-26] In one of the larger genome-wide association studies (GWAS) to date, Willour et al.[24] examined 1,200 individuals with BD who had attempted suicide and 1,497 BD non-attempters, finding no single nucleotide polymorphisms (SNPs) exceeding genome-wide significance for association. However, of 2,507 SNPs with $p<.001$ in the primary study, 49 replicated to $p<.01$ with the same direction of effect in an independent cohort of 1,295 attempters with BD and 1,822 non-attempters with BD.[24] It is unclear as to the genetic overlap between risk genes for psychiatric disorders and suicide attempts, although preliminary studies in small samples suggest partial pleiotropy.[25] Polygenic risk scores derived from the sum of individual

effects of many hundreds of BD-associated variants may help elucidate the relative contributions of genes versus environment for suicidal behaviors in BD.

Herein we examine ideation, attempts, and non-suicidal self-injury (NSSI) in 307 adolescent offspring/relatives of parents affected with BD (BD-relatives) as compared to 166 offspring/relatives of parents without specific psychiatric disorders (controls). The aims of the study were to assess whether: 1) BD-relatives are at greater risk of suicidal/self-harm behaviors than controls, independent of a personal history of mood or substance use disorders; 2) whether an individual's genetic risk for BD (i.e., polygenic risk score) is indicative of suicidal/self-harm behaviors; and 3) whether genetic risk for BD interacts with traumatic event exposures to increase risk for suicidal/self-harm behaviors, independent of the presence of a mood disorder or substance use disorders.

METHOD

Participants 12-21 years old were ascertained from five independent sites, four in the United States (Johns Hopkins University, University of Michigan, Washington University in St. Louis, and Indiana University[27]) and one in Australia (University of New South Wales).[28] All clinical procedures were approved by institutional review boards at the five centers. Written informed consent (or assent with parental consent for US participants <18 years old and Australian participants <17 years old) was obtained after a thorough explanation of the study. Participants were recruited using a "top-down" ascertainment method: that is, all offspring or other relatives in multiplex families of a proband with a confirmed *DSM-IV* diagnosis of bipolar disorder type-I (BP-I), type-II (BP-II), or schizoaffective disorder bipolar-type (SAB) who were in the age range 12-21 were eligible for inclusion, independent of the diagnostic status of the offspring. *DSM-IV* diagnosis was derived via the Diagnostic Interview for Genetic Studies

(DIGS)[29] and the Family Instrument for Genetic Studies (FIGS).[30] The BD-relatives were predominantly (88%) children of a proband with BD ascertained through the National Institute of Mental Health Genetics Initiative bipolar sample or similar genetic studies,[31-33] only 6% were siblings of a proband with BD, and 6% were second-degree relatives of a proband from multiplex families where a first-degree relative with BP-I/SAB also existed. Control participants were in the same age range but had no first-degree relative with a *DSM-IV* diagnosis of BP-I or BP-II, SAB, recurrent major depression (MDD), schizophrenia, recurrent substance abuse, or any past psychiatric hospitalization; and no parent with a first-degree relative who had a past mood disorder hospitalization or history of psychosis. Controls were recruited via general medical clinics, motor vehicle records, print and electronic media, and notice boards in universities and local communities. BD-relatives came from 199 families, 116 with a single offspring, 60 with 2 offspring, 16 with 3 offspring, 3 families with 4 offspring, and 1 family each with 5 and 6 offspring. Controls were from 120 families: 86 with a single offspring, 24 with 2 offspring, 9 with 3 offspring, and 1 family with 5 offspring.

Data were collected between June 1, 2006 and September 30, 2012. In families of BD-relatives and controls, all offspring were interviewed using the Kiddie Schedule for Affective Disorders (K-SADS)[34] and provided a blood specimen for DNA analysis. At least one parent had to be available for interview; parents were interviewed about themselves (using the DIGS), about their spouse and other relatives (using the FIGS), and about all offspring (using the K-SADS, Parent Version [K-SADS-P]).

Because existing versions of the K-SADS did not define specific episodes in time and duration before assessing symptoms and did not include questions targeting each *DSM-IV* criterion item for affective disorders, we adapted questions and interviewer instructions from the

DIGS to address these issues. The fully computerized K-SADS-BP is available at https://www.nimhgenetics.org/interviews/k-sads_bp_study55/index.php. Diagnoses were generated by best-estimate clinical consensus. Interviewers were extensively trained by the principal investigators and coordinators at each site after a weeklong common training at the Indiana University coordinating site. At each site, the interviewers or clinical coordinators had an extensive clinical background. Interviews were performed either in person or by telephone. The reliability of telephone interview for such purposes has been documented.[35] Clinicians performing the best-estimate diagnoses were not blinded to the BD-relative/control status of the participant,[36] but blind to the specific hypotheses of the study. Diagnoses and age at onset determinations were made on the basis of consensus between 2 clinicians (i.e., psychiatrists, clinical psychologists, or clinical social workers), including information from direct interview, medical records, and parent interview. Lifetime diagnoses were assigned according to *DSM-IV* criteria, including BP-NOS, which was generally diagnosed only if the participant approached the criteria for BP-II but had one fewer symptom in the hypomanic and depressive categories.

Measures

Dependent Variables. Lifetime occurrence of ideation, attempts, and NSSI were each studied independently over the course of follow-up, using data from all available K-SADS diagnostic assessments. NSSI is defined herein as the direct and deliberate infliction of pain or tissue damage without suicidal intent.[37] Most lifetime ideation, attempts, and NSSI were reported at baseline at a mean age of 17 years. From baseline to the end of follow-up, there were 17 additional incident reports of ideation, 7 incident reports of attempts, and 10 incident reports of NSSI.

Independent Variables, Psychiatric Diagnoses. Lifetime *DSM-IV* mood disorders (major

depression, bipolar disorder) and a variable including lifetime *DSM-IV* substance use disorder (i.e., alcohol abuse or dependence and drug abuse or dependence) were computed utilizing best-estimate diagnoses from the K-SADS.

Independent Variables, Traumatic Events. Traumatic event exposures were assessed through the Stressful Life Events Schedule child-reported (SLES-C) version,[38] which assesses the presence of over 80 possible stressors in the past 12 months. Three SLES variables were utilized to tap exposure to bullying, domestic violence, and sexual abuse – each known risk factors or correlates of ideation and attempt. Endorsement of any of the three SLES traumatic event exposures were computed into a fourth composite variable, named "any trauma history."

Genotyping and Quality Control. Peripheral blood samples were collected from all individuals for genetic analysis. DNA was extracted from whole blood by the Rutgers University Cell and DNA Repository (US participants) or Genetic Repositories Australia (Australian participants), as previously described.[39] Genome-wide SNP genotyping was conducted using the Infinium PsychArray BeadChip (Illumina, Scoresby, Victoria, Australia) at Mt. Sinai School of Medicine Genomics Core Facility, with genotype calling and quality control conducted using standard Psychiatric Genomics Consortium (PGC) pipelines. In brief, genotypes were called from three algorithms (birdseed, zCall, genCall) and SNPs with Hardy-Weinberg Equilibrium (HWE) p<1e-06 or genotype call rates < 97% removed, then resulting files merged in PLINK.[40] A second quality control was then applied to remove individuals with SNP call rates <98%, individuals with inbreeding coefficient FHET outside ±0.2 or genotype-derived sex discrepancy with recorded sex from clinical files. SNPs with minor allele frequency (MAF) <0.00001, and those with HWE p<1e-06 in controls or HWE p<1e-10 in cases were excluded, leaving 426,091 SNPs. The successfully genotyped SNPs had a >99.6% genotype pass rate.

Imputation and multidimensional scaling analysis to develop genotype-derived ethnicity principal components was conducted following the ENIGMA2 protocols (http://enigma.ini.usc.edu/). Briefly, post-QC genotype files were merged with genotypes from ethnically diverse 1000 genomes samples (Human Mapping Set, phase 1 release v3), using SNPs that are polymorphic in European populations. SNPs with MAF <0.01, genotype call rate <95%, strand ambiguity, and those with HWE p<1e-06 were excluded prior to haplotype phasing and imputation using mach and minimach.[41,42]

Multidimensional scaling analysis was conducted in PLINK using 164,680 independent SNPs across the panel, from which principal components were calculated. The principal components values from our sample were compared to those of participants of known ancestry to derive a genotype-derived ancestry allocation for each participant. Identity-by-descent (IBD) estimates were generated from 75,182 independent SNPs and were used to confirm documented familial relationships, identify any spurious relationships between participants, and identify gender discrepancies between genotype-derived and documented gender, resulting in subject exclusion.

Polygenic Risk Score (PRS) Determination. BD-associated SNPs were selected on the basis of prior evidence of genetic association from the PGC1-BD discovery sample.[23] Polygenic risk scores (PRS) were computed from index-SNPs after clumping based on linkage disequilibrium, using the --*score* function in PLINK,[40] and were weighted by the log odds ratio of the risk allele from the original discovery GWAS.[23] Prior to computing BD-PRS, strand-ambiguous SNPs, indels, and those with imputation r^2<0.8 were excluded. BD-PRS was tested at three increasingly liberal p-value thresholds: the first representing SNPs whose discovery p-value was less than .0001 ($BD\text{-}PRS_{p<0.0001}$; n=97 SNPs), the second representing SNPs whose

discovery p value was less than .001 (BD-PRS$_{p<0.001}$; n=97+440 SNPs), and the third representing SNPs whose discovery p value was less than .01 (BD-PRS$_{p<0.01}$; n=3,011 SNPs; 97+440+2,474 SNPs). Participants were dichotomized into a high or low BD-PRS category for statistical analysis, where high BD-PRS represents the top 2 quintiles and low BD-PRS represents the bottom 3 quintiles.

Demographic Characteristics

Age, sex, and ethnicity were determined at baseline interview. Self-reported ethnicity, using the 7 United States Census categories, was consistent with genotype-derived ethnicity (98.7% concordance). Based on genotype-derived ethnicity, participants were categorized as Caucasian, African, or Other. Caucasian and African groups were used as covariates in the analyses each compared to the other ethnic group. In order to explore whether our findings were subject to confounding by ethnicity, we conducted analyses in Caucasians only.

Statistical Analyses

Demographic and clinical characteristics were compared between BD-relatives (n=307) and controls (n=166), as well as those with and without suicidal ideation, attempts, and NSSI using generalized estimating equations (GEE) models[43-44] implemented in R software (https://www.r-project.org/). GEE enables specifying a binomial distribution for the outcome, and an exchangeable clustering pattern within family to correct for non-independence of measurement between siblings. This modeling approach was also implemented to test whether a high BD-PRS is predictive of ideation, attempts, and NSSI and whether it interacts with traumatic event exposures, adjusting for BD-relative status, ethnicity, and the presence of *DSM-IV* mood disorders and substance use disorders. Interactions between BD-PRS high/low category and trauma exposure were estimated for models with significant main effects. All models using

the BD-PRS included adjustment for the genetically-informed ethnicity variables.

RESULTS

The demographic and clinical characteristics of the BD-relative and control groups are described in Table 1. The BD-relative and control groups were gender balanced and were mainly of European ancestry (85% vs. 65% for BD-relative and control groups, p<.001). At the time of baseline interview, the mean age of BD-relatives was slightly younger than the control group (16.7 vs. 17.1 years, p=.029). As expected, BD-relatives were more likely to have a *DSM-IV* lifetime mood disorder (OR=1.4, 95% CI=1.2-1.6, p<.001) and lifetime substance use disorder (OR=1.2, 95% CI=1.1-1.3, p=.006).

BD-relatives were 30% more likely to have ideation and attempts than controls (OR=1.3, 95% CI=1.1-1.5, p<.001; and OR=1.3, 95% CI=1.1-1.5, p=.003; respectively) but were not more likely to have NSSI (OR=1.1, 95% CI=0.9-1.2, p=.192). There were no group differences between BD-relatives and controls in exposure to domestic violence, sexual abuse, being bullied, or a composite measure of any traumatic event exposure.

After adjusting for offspring mood and substance use disorders and demographic factors in the full sample, ideation and attempts were both significantly more prevalent in BD-relatives (OR=1.1, 95% CI=1.0-1.1, p=.012; and OR=1.1, 95% CI=1.0-1.2, p=.011), as compared to controls (Table 2). NSSI did not differ between BD-relatives and controls. In the sample of Caucasian-only participants, ideation and attempts were more common in BD-relatives than controls after adjusting for demographic variables (model 2), but did not remain significant after adjusting for offspring mood and substance use disorders (data not shown).

Table 3 shows results of GEE analyses comparing those with and without ideation, attempts, and NSSI. Those with and without ideation, attempts, and NSSI did not differ

according to sex or baseline age. Caucasian participants were less likely to report ideation, attempts, and NSSI. Those with ideation were more likely to a have a mood disorder than those without (OR=17.7, 95% CI=8.3-37.7, p<.001), as were attempters versus non-attempters (OR=12.1, 95% CI=4.1-35.3, p<.001), and those with NSSI versus those without NSSI (OR=20.5, 95% CI=9.3-45.2; p<.001). Those with ideation were more likely than those without ideation to have a substance use disorder (OR=3.0, 95% CI=1.7-5.3, p<.001), as were attempters versus non-attempters (OR=4.9, 95% CI=2.2-10.8, p<.001), and those with NSSI versus those without NSSI (OR=2.8, 95% CI=1.5-5.0, p<.001). The only trauma history construct that was associated with any of the three suicide behavior outcomes was that any trauma history was two-fold higher in suicide attempters than in non-attempters (OR=2.1, 95% CI=1.2-3.8, p=.014).

Using the SNPs most robustly associated with BD from the PGC, we conducted analyses to determine whether a BD-PRS was higher in those with suicidal/self-harm behaviors compared to those with no suicidal/self-harm behaviors. Among participants of all ethnic backgrounds, BD-relatives were more likely to have a higher BD-PRS than controls at the p <.001 and p<.01 thresholds ($BD\text{-}PRS_{p<0.001}$ OR=1.1, 95% CI=1.0- 1.2, p=.030; and $BD\text{-}PRS_{p<0.01}$ OR=1.2, 95% CI=1.1-1.3, p=.001), after adjusting for age, sex, principal component analysis (PCA) ethnicity, mood and substance use disorders (Table 4). Those with higher BD-PRS at p<.01 were marginally more likely to have attempted suicide, after adjusting for BD-relative/control group, age, sex, PCA ethnicity and mood and substance use disorders (OR=2.3, 95% CI=1.0-5.4, p=.061). However, the mean BD-PRS did not differ between those with and without ideation or NSSI at any p-value threshold.

Because the PGC discovery cohort was largely ethnically Caucasian, computation of BD-PRS for ethnically diverse participants may result in distortion of the PRS due to ethnically

heterogeneous odds ratios and allele frequencies. Therefore, we repeated all BD-PRS analyses in Caucasian-only participants, representing around 80% of the full sample. BD-relatives were again more likely to have a higher BD-PRS than controls at p <.001 and p<.01 (OR=1.2, 95% CI=1.0-1.4, p=.035; and OR=1.2, 95% CI=1.0-1.5, p=.039; respectively) after adjusting for BD-relative/control group, age, sex, ethnicity, mood and substance use disorders. However, among the smaller Caucasian-only sample (80% of the sample), odds ratios were not statistically significant for ideation, attempts, and NSSI (Table 4).

To evaluate interactions of BD-PRS with trauma on the risk for suicide outcomes and relative status, we chose a single p-value discovery threshold of p<.001. Interestingly, for those participants who experienced trauma exposure and had a high BD-$PRS_{p<.001}$, the risk for suicide attempt was significantly elevated after adjusting for sex, baseline age, BD-relative/control group, ethnicity, lifetime *DSM-IV* mood disorders and substance use disorders (OR=3.2, 95% CI=1.1-9.4, p=.037) (Table 5). Stronger effects were observed in the Caucasian-only analysis (OR=5.4, 95% CI=1.5-20.0, p=.011, data not shown) adjusting for demographic characteristics, mood disorders, and substance use disorders.

DISCUSSION

This study uniquely examines suicidal and self-harm behaviors in a young cohort of individuals who are at increased risk of BD, but many of whom have not yet developed BD themselves. We found that offspring of BD-relatives report more suicidal ideation and attempts than controls. This finding was sustained after adjusting for the presence of mood disorders and substance use disorders, suggesting that parental BD is a key correlate of suicidal ideation and attempts, and that genetic risk for suicidal behavior is not wholly acting through a genetic pathway for mood disorder. Importantly, we find that a high BD-PRS plus traumatic event

exposure is associated with increased suicide attempts, independent of mood or substance use disorders and ethnicity. This could imply that trauma exposure increases the risk of attempts especially among those at genetic risk, regardless of presence of mood disorders.

To our knowledge, no prior studies have examined the relationship between BD-PRS and suicide attempt, let alone an interaction with traumatic events. The most permissive BD-PRS (derived from SNPs at $p < .01$) marginally differentiated those with and without attempts, independent of relatives status, PCA ethnicity, and mood and substance use disorders, whereas the more restrictive PRS did not. This may indicate that other genetically mediated aspects common to both BD and suicide behavior could be contributing, such as impulsivity, aggression, or severity of social, cognitive, or psychiatric impairment. Indeed, these pleiotropic effects may be more apparent in PRS derived from a larger number of variants, which will more likely encompass risk variants for BD as well as impulsive traits. The lack of association in the Caucasian-only analysis may indicate that population stratification is driving the association with suicide attempt in the larger more ethnically diverse sample, or that it is influenced by the loss of sample size, resulting in reduced power to detect significant differences. As the effect sizes in the Caucasian-only analysis are similar, the smaller sample size appears to be influencing those results, thus replication in a larger ethnically homogeneous cohort are warranted. Identification of specific genes influencing suicide attempt and exploration of genetic pleiotropy between BD and suicide attempt will soon be possible, pending the large-scale genome-wide association analysis of suicide attempt currently underway as part of the Psychiatric Genomics Consortium.

There is a dearth of information on the link between NSSI and BD, although it has been reported that the risk factors for NSSI are similar to those for suicide attempts in young people.[45,46] Intent to die is not evident in NSSI, and the motives behind NSSI and suicide

attempts differ.[47] Small clinical studies have found an increase in NSSI among those with BD,[48-49] yet a recent meta-analysis on risk factors for NSSI did not find an association between NSSI and BD.[50] NSSI had some different correlates than suicidal ideation and attempts in our study, as NSSI was associated with sex and age at interview, but not trauma exposure. Unlike suicidal ideation and attempts, NSSI was not significantly higher in BD-relatives than controls in the univariate model.

We should acknowledge the limitations of the present observations. First, even in a high-risk study, suicide attempts and exposures to trauma were relatively uncommon in our sample, thus a composite trauma exposure was used. Second, the assessment of childhood diagnoses rests on a combination of retrospective data from child and parental observations, supplemented with medical records when available. Third, we applied a genetic model that assumes additivity of risk alleles in a single aggregate score as per the methods used by the PGC.[22] Fourth, measurement of trauma/stress (SLES) was over the 12 months prior to the baseline assessment, whereas the occurrence of SA, SI, and NSSI is a lifetime evaluation. The counterbalancing strengths are that this study includes well-characterized, at-risk youth from a genetically informative sample.

Schaffer et al.,[6] as part of the International Society for Bipolar Disorders Task Force on Suicide meta-analysis, notes the importance of integrating genetic, epigenetic, and social learning mechanisms when building models of psychobiological contributors to suicidal behaviors in BD. Early-life adversity and epigenetic mechanisms seem to be related to causal mechanisms for this diathesis. *SKA2* DNA methylation mediates HPA-axis responsivity in the context of childhood trauma[51] and has been associated with a range of HPA-axis related psychopathology including posttraumatic stress disorder[52] and suicidal behavior.[51,53] Biomarkers

might help to inform risk-assessment procedures and treatment choice for the prevention of suicide.

Clinical Guidance:

- We found that offspring of individuals with BD are at risk for suicidal attempts and ideation, but not only through specific mechanisms associated with mood disorder vulnerability.
- We also found that genetic susceptibility to BD can increase the risk for suicide attempt, but only among those who also have experienced trauma.
- This work highlights the importance of severe environmental stressors in the development of suicide attempts in those at risk for bipolar disorder.

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Table 1. Demographic and Clinical Characteristics of the Sample

	BD-Relatives n=307		*Controls n=166*		*(OR)*	*95% CI*	*p Value*
	#	%	#	%			
Demographics							
Female	152	50%	79	48%	0.9	0.9-1.1	.929
Caucasian	**261**	**85%**	**108**	**65%**	**2.8**	**1.5-5.3**	**.001**
Age at baseline	**16.7**	**sd=3.0**	**17.1**	**sd=2.7**	**0.9**	**0.9-0.9**	**.029**
Axis I diagnoses							
Mood disorder	**152**	**50%**	**36**	**22%**	**1.4**	**1.2-1.6**	**<.001**
Substance disorder	**91**	**30%**	**29**	**17%**	**1.2**	**1.1-1.3**	**.006**
Conduct disorder	**13**	**5%**	**1**	**0.01%**	**1.4**	**1.3-1.8**	**.0156**
ADHD	17	6.5%	4	03%	1.1	0.95-1.3	.191
Self-injurious thoughts/behaviors							
Ideation	**72**	**23%**	**15**	**9%**	**1.3**	**1.1-1.5**	**<.001**
Attempt	**34**	**11%**	**6**	**4%**	**1.3**	**1.1-1.5**	**.003**
NSSI	55	18%	22	13%	1.1	0.9-1.2	.192
Trauma history							
Domestic violence	24	8%	5	3%	0.9	0.8-1.0	.217
Sexual abuse	12	4%	4	2%	0.9	0.8-1.0	.176
Bullied	45	15%	15	9%	0.9	0.9-1.0	.324
Any trauma history	69	22%	23	14%	1.0	0.9-1.1	.657

Note: Statistics include no covariates. Bold text indicates statistical significance at p<.05. ADHD = attention-deficit/hyperactivity disorder; NSSI = nonsuicidal self-injury.

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Table 2. Unadjusted and Adjusted Generalized Estimating Equations Analyses of Relative Status on Lifetime Ideation, Attempt, and Non-Suicidal Self-Injury (NSSI)

	Model 1			*Model 2*			*Model 3*		
	OR	95% CI	p Value	OR	95% CI	p Value	OR	95% CI	p Value
All Participants									
ideation	**1.3**	**1.1-1.5**	**<.001**	**1.2**	**1.1-1.3**	**<.001**	**1.1**	**1.0-1.1**	**.012**
attempts	**1.3**	**1.1-1.5**	**.003**	**1.3**	**1.1-1.6**	**<.001**	**1.1**	**1.0-1.2**	**.011**
NSSI	1.1	0.9-1.2	.192	**1.1**	**1.0-1.2**	**.016**	1.0	0.9-1.1	.173

Note: Results in boldface are statistically significant. Model 1: Unadjusted. 307 individuals with bipolar disorder (BD) relatives out of 473 individuals. Model 2: Adjusted for demographics (age, sex, and ethnicity). 286 individuals with relatives with BD out of 432 individuals. Model 3: Adjusted for demographics, mood disorders, and substance use disorders. 283 individuals with relatives with BD out of 422 individuals.

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Table 3. Characteristics of Those With Ideation, Attempt, and Non-Suicidal Self-Injury (NSSI)

	Ideation *n=87 versus 336 with no ideation, attempt or NSSI*			*Attempt* *n=40 versus 336 with no ideation, attempt or NSSI*			*NSSI* *n=77 versus 336 with no ideation, attempt or NSSI*		
	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Demographics									
Female	0.9	0.5-1.7	.775	0.9	0.4-1.9	.729	1.3	0.7-2.5	.392
Caucasian	**0.3**	**0.1-0.9**	**.029**	**0.1**	**0.2-0.4**	**.001**	**0.3**	**0.1-0.9**	**.040**
Age at baseline	1.0	0.9-1.1	.918	1.0	0.8-1.1	.515	1.1	0.9-1.2	.105
Axis I Diagnoses									
Mood disorder	**17.7**	**8.3-37.7**	**<.001**	**12.1**	**4.1-35.3**	**<.001**	**20.5**	**9.3-45.2**	**<.001**
Substance use disorder	**3.0**	**1.7-5.3**	**<.001**	**4.9**	**2.2-10.8**	**<.001**	**2.8**	**1.5-5.0**	**<.001**
Traumatic stress history									
Domestic violence	0.9	0.6-1.4	.550	1.3	0.7-2.4	.379	0.9	0.5-1.3	.408
Sexual abuse	0.9	0.5-1.4	.597	1.5	0.8-2.8	.163	0.9	0.6-1.4	.642
Bullied	1.2	0.8-1.8	.394	1.4	0.8-2.6	.231	0.9	0.6-1.4	.701
Any trauma history	1.3	0.8-2.0	.252	**2.1**	**1.2-3.8**	**.014**	0.9	0.6-1.4	.743

Note: Results in boldface are statistically significant. Generalized estimating equations analyses adjusted by demographics, mood and substance use disorders, and past-year traumatic stress history.

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Table 4. Bipolar Disorder Polygenic Risk Score Associations

	p-value threshold <.0001			*p-value threshold <.001*			*p-value threshold <.01*		
	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value
All (n/N)									
Ideation (79/386)	1.0	0.5-1.8	.914	0.9	0.5-1.6	.720	1.3	0.7-2.4	.367
Attempt (35/342)	0.5	0.2-1-3	.169	1.2	0.5-2.6	.669	2.3	1.0-5.4	.061
NSSI (75/382)	1.0	0.5-1.9	.943	1.1	0.6-2.0	.788	1.3	0.7-2.5	.420
Relative Status (283/431)	1.0	0.9-1.1	.275	**1.1**	**1.0-1.2**	**.030**	**1.2**	**1.1-1.3**	**.001**
Caucasian									
Ideation (68/328)	1.1	0.6-2.2	.745	0.9	0.5-1.6	.671	1.1	0.6-2.1	.714
Attempt (26/286)	0.6	0.2-1.8	.388	1.1	0.5-2.6	.787	1.5	0.6-3.4	.354
NSSI (59/319)	1.1	0.5-2.3	.775	1.0	0.5-2.0	.932	1.1	0.6-2.1	.775
Relative Status (255/362)	1.0	0.9-1.2	.755	**1.2**	**1.0-1.4**	**.035**	**1.2**	**1.0-1.5**	**.039**

Note: Results in boldface are statistically significant. Models for suicide/non-suicidal self-injury (NSSI) outcomes adjusted for sex, age, ethnicity, mood disorders, substance use disorders, and relative status.

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Table 5. Results of Polygenic Risk Score by Trauma Exposure Interaction

	No Trauma			Trauma			
	OR	**95% CI**	**P value**	**OR**	**95% CI**	**P value**	**Interaction P value [c]**
Relatives [a]							
With Low PRS: (191/296)	1.1	1.0-1.3	.066				
With High PRS: (92/135)				1.3	0.9,1.7	.125	.545
Ideation [b]							
With Low PRS: (40/266)	0.78	0.3-1.3	.553				
With High PRS: (39/120)				1.1	0.4,1.2	.844	.348
Attempt [b]							
With Low PRS: (12/238)	0.27	0.05,1.4	.111				
With High PRS: (23/104)				2.7	0.9, 8.3	.089	**.041**
NSSI [b]							
With Low PRS: (48/274)	0.80	0.4, 1.8	.574				
With High PRS: (27/108)				1.1	0.3, 3.9	.883	.220

Note: Results in boldface are statistically significant. Bipolar disorder-polygenic risk score (BD-PRS) p-value threshold is .001. NSSI = nonsuicidal self-injury.

[a] Adjusted for demographics, and mood disorders and substance use disorders

[b] Adjusted for demographics, BD-relatives status, and mood and substance use disorders

[c] Interaction p-value is computed using the full sample and reflects the increased risk in the outcome for those with both trauma and high BD-PRS compared to those with no trauma and low BD-PRS.

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Traumatic Stress Interacts with Bipolar Disorder Genetic Risk to Increase Risk for Suicide Attempts

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